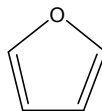


FURAN
CAS No. 110-00-9

First Listed in the *Eighth Report on Carcinogens*



CARCINOGENICITY

Furan is *reasonably anticipated to be a human carcinogen* based on evidence of malignant tumor formation at multiple tissue sites in multiple species of experimental animals (reviewed in IARC V.63, 1995).

When administered by gavage, furan induced an increase in the incidence of hepatic cholangiocarcinoma, hepatocellular adenoma, hepatocellular carcinoma, and mononuclear cell leukemia in male and female F344/N rats treated for up to 2 years (NTP, 1993). Gavage administration of furan to male F344 rats for 9, 12, or 13 months resulted in high incidences of cholangiocarcinoma by 16 months after cessation of treatment (Maronpot et al., 1991; Elmore and Sirica, 1993). When administered by gavage, furan induced a dose-dependent increase in the incidence of hepatocellular adenoma and carcinoma and benign pheochromocytoma in male and female B6C3F1 mice treated up to 2 years (NTP, 1993).

There is no adequate data available to evaluate the carcinogenicity of furan in humans.

ADDITIONAL INFORMATION RELEVANT TO CARCINOGENESIS OR POSSIBLE MECHANISMS OF CARCINOGENESIS

In bacteria, furan induced gene mutations in *Salmonella typhimurium* strain TA100 (Lee et al., 1994) and in *E. coli* containing bacteriophage T7 (Ronto et al., 1992), but not in *S. typhimurium* strains TA98 (Lee et al., 1994), TA1535, or TA1537 (Mortelmans et al., 1986). In *Drosophila melanogaster*, it did not induce gene mutations (Foureman et al., 1994). In mammalian *in vitro* systems, it induced gene mutations in mouse lymphoma cells (McGregor et al., 1988), DNA damage in Chinese hamster ovary (CHO) cells (NTP, 1993), and chromosomal damage in CHO cells with an exogenous metabolic activation system (NTP, 1993; Stich et al., 1981; cited by IARC V.63, 1995), but it did not induce DNA damage in mouse or rat hepatocytes (Wilson et al., 1992; NTP, 1993). In mammalian *in vivo* systems, furan induced chromosomal aberrations in bone marrow of B6C3F1 mice (NTP, 1993), but did not induce DNA damage in bone marrow or hepatocytes of B6C3F1 mice (Wilson et al., 1992; NTP, 1993) or hepatocytes of F344/CrIBr rats (Wilson et al., 1992).

A current hypothesis for the mechanism of furan-induced carcinogenesis is metabolic activation of furan by cytochrome P-450 to a reactive and cytotoxic intermediate that stimulates cell replication, increasing the likelihood of tumor induction (Chen et al., 1995; Kedderis et al., 1993). The postulated reactive metabolite is *cis*-2-butene-1,4-dial, which was recently characterized as a furan metabolite by Chen et al. (1995). This reactive metabolite probably explains furan's binding reactivity with proteins both *in vitro* (uninduced and induced F344 male rat liver microsomes) and *in vivo* (F344 male rat liver protein) in biological systems (Burka et al., 1991; Parmar and Burka, 1993). Furan metabolites may react with DNA, but Burka et al. (1991)

did not detect any radiotracer in DNA from livers of rats treated with [^{14}C]furan. No data are available that would suggest that the mechanisms thought to account for tumor induction by furan in experimental animals would not also operate in humans.

PROPERTIES

Furan, which is classified as a cyclic, dienic ether, is a clear, colorless, flammable liquid with an ethereal odor. Although it will turn brown while standing in air, the addition of a small amount of water will retard color change. Unless stabilized, furan will react slowly with air to form an unstable, explosion-prone peroxide. Furan boils at 32°C, freezes at -85.6°C, and has a specific gravity of 0.9371 at 758 mm mercury. It is insoluble in water but is soluble in alcohol, ether, and most common organic solvents including acetone, benzene, toluene, petroleum, ether, and chloroform. When heated to decomposition, furan emits acrid smoke and irritating fumes.

USE

Furan is used primarily as an intermediate in the synthesis and production of other organic compounds. Hydrogenation of furan over a nickel catalyst produces high yields of tetrahydrofuran and is a source of commercial tetrahydrofuran (McKillip and Sherman, 1980, and McKillip et al., 1989; both cited by IARC V. 65, 1995; NTP, 1991). Furan may also be used as a starting material in the commercial production of thiophene. Furan is used in the formation of lacquers and as a solvent for resins. It is also used in the production of agricultural chemicals (insecticides), stabilizers, and pharmaceuticals (McKillip and Sherman, 1980, and McKillip et al., 1989; both cited by IARC V. 65, 1995).

PRODUCTION

One company in the United States produces furan (SRI, 1996). Commercial production of furan involves decarbonylation of furfural over a palladium/charcoal catalyst (McKillip et al., 1989; cited by IARC, 1995). No data on imports or exports of furan were available. Chem Sources (1996) identified 21 U.S. suppliers.

EXPOSURE

The primary route of potential human exposure to furan is inhalation. Since the industrial processes in which furan are used are conducted in closed systems and its volatility requires that furan be handled in closed containers, occupational exposure is limited (NTP, 1991). The National Occupational Hazard Survey, conducted by NIOSH from 1972 to 1974, estimated that 244 workers were potentially exposed to furan in the workplace (NIOSH, 1976). The National Occupational Exposure Survey (1981-1983) indicated that 35 workers, including 7 women, were potentially exposed to furan (NIOSH, 1984). The pattern of commercial use suggests that minimal exposure to the general public would be expected through contact with products contaminated with furan (NTP, 1991).

Furan was detected in the indoor air of homes in the Chicago and Washington D.C. metropolitan areas (Jarke et al., 1981). Furan was detected in waste gases during drying of molassed beet pulp (Oldfield et al., 1979 abstract). Furan was detected in 1 of 63 industrial effluents at a concentration of < 10 µg/L (Perry et al., 1979; cited by IARC V. 65, 1995). It was

also found at a concentration of 7 ± 4 ppb ($\mu\text{g/L}$) in aqueous condensate samples from low-temperature gasification of rosebud coal (Pellizari et al., 1982). Furan was detected in a creek in the Niagara River watershed (Elder et al., 1981) and in the Niagara River itself (Howard et al., 1990; cited by IARC V. 65, 1995).

Furan is released as a gas-phase component of wood smoke, cigarette smoke, and exhaust gas from diesel and gasoline engines (Howard et al., 1990; cited by IARC V. 65, 1995). In Flanders, a study of nuisance odors showed a concentration of $170 \mu\text{g furan/m}^3$ was detected from the emissions of a deep fat frier (Moortgat et al., 1992; cited by IARC, 1995).

Furan has been identified in cooked beef aroma (Galt and MacLeod, 1984) and in the breast milk of 1 of 8 lactating women in hospitals and clinics in Louisiana, New Jersey, and Pennsylvania (Pellizzari et al., 1982).

In the expired air of cigarette smokers, furan has been detected at 0 to $98 \mu\text{g/h}$, while in nonsmokers, it has been detected in the breath at 0 to $28 \mu\text{g/h}$ (Howard et al., 1990; cited by IARC V. 65, 1995). Furan was detected in expired air in 6 of 8 volunteer male subjects at concentrations ranging from 0.25 to $98.0 \mu\text{g/h}$. Both the highest and lowest concentrations were detected in smokers (Conkle et al., 1975).

REGULATIONS

EPA regulates furan under the Resource Conservation and Recovery Act (RCRA); Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA); Superfund Amendments and Reauthorization Act (SARA); and the Toxic Substances Control Act (TSCA). EPA has established rules for regulating hazardous spills and for reporting such spills or releases. EPA has also set general threshold amounts, and established requirements for handling and disposal of furan wastes. Furan is regulated as a hazardous constituent of waste under RCRA and is subject to report/recordkeeping requirements under RCRA and SARA. A statutory reportable quantity (RQ) of 1 lb was established for furan, but EPA increased the RQ to 100 lb under CERCLA. The Department of Transportation (DOT) has its own regulations for the transportation of furan in tank cars and tank trucks. OSHA regulates furan under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table B-66.